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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,444	COHEN ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 5, 2008, has been entered.

3. The amendment filed December 5, 2008, is acknowledged and has been entered. Claims 2, 3, 10, 12 and 14-17 have been canceled.

4. Claims 1 and 4-8 are pending in the application and are under examination.

Election/Restrictions

5. Upon further consideration of the restriction and election requirement set forth in the Office action mailed April 4, 2006, the various species of the invention of Group I, wherein said agent is an anti-emetic, a cancer vaccine, an anti-vascular agent and an anti-proliferative agent has been rejoined with the elected agent species of the invention, wherein said agent is an analgesic.

However, Applicant has further elected the following species of invention wherein the vaccine is an "autologous tumor vaccine"; the anti-proliferative agent is a "PDGFR inhibitor"; the antibody is "2.13.2"; the VH gene is "VH DP-47; and the VL gene is "A30" -- no other species of the elected invention has been rejoined. Due to the Applicant's cancellation of claim 9, the VH and VL gene species election is currently moot.

Response to Amendment

6. The amendment filed on December 5, 2008, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiencies in replying to this Office action:

The amendment to the claims filed December 5, 2008, is non-compliant because the amendment does not properly present markings to show only the changes made in the current amendment relative to the immediate prior version. For example, while claim 4 recites “ondansetron, hydrochloride” in the instant amendment, the immediate prior version recited of “ondansetron hydrochloride", and the addition of the “,” was not properly demarcated as required by 37 CFR § 1.121. Also while claim 8 previously contained a period, it is missing a period in the instant amendment and this change is not properly demarcated as required by 37 CFR § 1.121.

Briefly, the revised amendment practice now requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled", "withdrawn", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., strikethrough); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). The text of "canceled" and "not entered" claims must not be presented; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

Applicant is reminded: Only the corrected section(s) of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

Priority

7. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of US provisional application 60/447353, filed 2/13/03, is acknowledged.

However, claims 1 and 4-8 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely February 10, 2004.

Response to Arguments

8. Applicant's arguments with respect to the rejections of the claims under 35 U.S.C. §103(a) for the reasons set forth in the preceding Office action have been carefully and fully considered but are moot in view of the following new grounds of rejection and the withdrawal of the previous grounds of rejection of the claims under 35 U.S.C. §103(a).

Grounds of Objection and Rejection Withdrawn

9. The grounds of rejection set forth in the previous Office action mailed September 5, 2008, have been withdrawn in view of the following new grounds of rejection.

Specification

10. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is REACTI-BIND™ (see e.g., page 20).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

11. Claims 1 and 4-8 are objected to because the claims are drawn in the alternative to the subject matter of a non-elected invention or a non-elected species of invention.

12. Claim 4 is objected to for reciting “ondansetron, hydrochloride”. It appears that the addition of a comma is a typographical error because this change was not properly made and the specification only sets forth the anti-emetic ““ondansetron hydrochloride) (see Page 3).

13. Claim 8 is objected to for not ending in a period.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1 and 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1 and 4-8 are also vague and indefinite in the recitation "2.13.2" as the sole means of identifying the antibody or antibodies to which the claims are directed. The use of laboratory designations to identify a particular antibody renders the claims indefinite because different laboratories may use the same laboratory designations to define completely different antibodies. For example, as evidenced by US 20080124339 A1 (Pullen et al, 2008; see e.g., paragraph [0052]) antibodies produced by hybridomas are commonly given numerical designations in a format similar to the one recited and thus the use of a laboratory designation alone cannot suffice to clearly and particularly identify the antibody referred to in the claims.

This rejection can be overcome by amending the claims to specifically and uniquely identify the 2.13.2 antibody, for example, by reciting that 2.13.2 comprise a heavy and light chain comprising the amino acid sequences of SEQ ID NO:45 and 47,

respectively (see page 22, lines 20-25 of the specification which discloses a 2.13.2 antibody comprising these sequences).

(b) Claims 1 and 4-8 are indefinite because claims 1 recites the phrase "effective amount". The metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, where the claims recite the phrase "effective amount", yet fail to state the function that is necessarily achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

In this instance, while the claim recites the intended use for the treatment of multiple myeloma, the mammal need not have been diagnosed with multiple myeloma and the specification teaches at page 2 that the "present invention relates to a method for the treatment or prevention of a disorder wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated auto-immune disease, endocronological disorder, ischemia, and neurodegenerative disorder in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody that is effective in treating said disorder".

Accordingly, in this instance, the claims are indefinite because it cannot be ascertained to which beneficial or desired results the claims are directed, and it is therefore uncertain what result the effective amount of the antibody must be capable of achieving because the mammal need not have any disorder. The various endpoints and extents that define effective treatment are of a more conditional or qualitative nature. So, while the amount most be effective, it is not immediately evident what effect is necessarily achieved? Therefore, t is submitted that the expected or desired effect that is to be achieved in the practice of the claimed invention to treat cancer, unless more particularly defined, is highly subjective and would tend to vary substantially; and accordingly, the claims fail to delineate with the requisite clarity and particularity the metes and bounds of the invention, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claims 1 and 4-8 are indefinite because claim 1 is directed to a method for the treatment of multiple myeloma; yet the claim merely recites the administering a 2.13.2 antibody to a mammal in combination with another agent. There is no process

step that clearly relates back to the purpose or objective of the claimed invention; consequently, the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of the claim. Thus, in the absence of a correlative step positively relating the whole of the process to its intended use, as recited in the preamble, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(d) Claim 5 is indefinite for being drawn to the method of claim 1 comprising "administering said antibody in combination with a **vaccine**". In this case, claim 1 recites administering a 2.13.2 antibody in combination with an agent selected from the group consisting of a corticosteroid, anti-emetic, **cancer vaccine**, analgesic, anti-vascular agent, and anti-proliferative agent. Therefore, reciting a method of administering said antibody in combination with a **vaccine** lacks antecedent basis as claim 1 only recites that a cancer vaccine can be selected. Therefore, it is unclear whether "administering said antibody in combination with a **vaccine**" is meant to refer to and limit the cancer vaccine of claim 1 or if another different vaccine is administered in combination with the method of claim 1 as well. Accordingly, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

Furthermore, the Federal Circuit has commented that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). See *Noelle v. Lederman*, 69 USPQ2d 1508 (CAFC 2004).

Finally, with further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are broadly drawn to a diverse genus of methods that administer a structurally and functionally diverse genus of antibodies designated “2.13.2” in an effective amount to a mammal in combination with an agent selected from the group consisting of a anti-emetic, cancer vaccine, analgesic, anti-vascular agent, and anti-proliferative agent with the stated objective of “treating” multiple myeloma. As drawn to the elected species of "vaccine" claim 5, recites administering a structurally and functionally diverse genus of “autologous tumor vaccines”. As drawn to the elected species of "anti-proliferative agent" claim 8, recites administering a structurally and functionally diverse genus of “PDGFR inhibitors”.

Notably, the scope of the term “treating” is being broadly, but reasonably interpreted as including “preventing” any disorder because the mammal need not have any disorder and in light of the following disclosure at page 6 which sets forth that treating encompasses preventing:

> The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or **preventing** the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

As a first point, the specification has not adequately described the genus of "2.13.2" antibodies that that would be effective prevent any disorder such as multiple myeloma.

In this case, the prevention multiple myeloma, i.e., keeping individuals free of any multiple myeloma indefinitely, is an intractable proposition, if not now wholly impossible, given, for example, that multiple myeloma is a heterogeneous disease, having widely varying pathologies and etiologies, and that its causes are multifactorial and as yet only partially characterized and poorly understood. It is generally recognized that a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development by any cause. Notably, in this case, the specification presents merely prophetic examples that administering to a mammal a "2.13.2" in combination with one of the recited agents would be effective to prevent multiple myeloma (see e.g., page 2). Accordingly, because one of skill in the art could immediately envision, recognize or predict whether any "2.13.2" antibody could prevent multiple myeloma, one of skill in the art would not recognize that Applicant was in possession of the claimed methods.

Secondly, with respect to the structurally and functionally diverse genus of "2.13.2" antibodies, the scope of the term "2.13.2" is being interpreted in light of the disclosure at page 17 that "Particular antibodies useful in practice of the invention include those described in WO 02/053596, which further describes antibodies 2.12.1, 2.13.2., 2.14.3, 3.1.1, 4.9.2, and 4.17.3."

In this case, WO 02/053596 (of record) exemplifies many structurally and functionally different 2.13.2 antibodies as it teaches at page 13 that "As used herein, an antibody that is referred to as, e.g., 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3 and 6.1.1, is an antibody that is derived from the hybridoma of the same name. For example, antibody

2.12.1 is derived from hybridoma 2.12.1". WO 02/053596 further exemplifies variations of "derived" antibodies, such as humanized, chimeric or human antibodies, that do not have any particularly identifying structural feature which would allow one of skill in the art to immediately envision or recognize a "2.13.2" antibody from any other. For example, at page 14, WO 02/053596 teaches that the term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. However, antibodies comprise multiple "regions" that are not responsible for antigen binding, such as framework regions, or Fc regions and therefore, it is apparent the "2.13.2" antibodies recited in the claim does not need to comprise any particularly identifying structural feature that correlates with its ability to be effective in treating any disorder.

To elaborate on why the humanized, chimeric or human antibodies and antigen binding fragments thereof which are encompassed by the term "2.13.2" lack adequate written description, Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that a naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

In view of Mariuzza et al., it is apparent that humanized or chimeric antibodies having less than all six CDRs that form the antigen binding site of a monoclonal antibody in their proper context of heavy and light chain variable domains does not suffice to describe the particularly identifying structural feature of the antibody that correlates with the antibody's ability to bind to the antigen bound by the monoclonal antibody. Absent a description of the at least minimal structural features correlating with a functional ability to bind to a particular antigen, which are shared by members of a

genus commonly sharing this function, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other antibodies. For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Furthermore, while the specification does adequately describe a 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a light chain comprising the amino acid sequence of SEQ ID NO:47, which binds to the human IGF-IR antigen (see e.g., page 1 and page 22), it is noted that the specification only establishes that this antibody is effective in inhibiting the progress of tumors expressing this antigen. One of skill in the art could not immediately envision, recognize or predict whether this antibody would be effective in any mammal to inhibit the progress of multiple myeloma in any mammal with multiple myeloma not expressing this antigen, and because the claims broadly encompass administering a "2.13.2" antibody to any mammal, one of skill in the art would not recognize that Applicant was in possession of the claimed methods for this reason as well.

Accordingly, in this case it is submitted that, because the specification only describes a 2.13.2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:45 and a light chain comprising the amino acid sequence of SEQ ID NO:47, the claimed methods have not been adequately described.

Then to address the written description of "cancer vaccines" or "autologous tumor vaccine" set forth in the claimed methods which are to be used in combination with a 2.13.2 antibody, while the art is replete with attempts to use autologous cancer cell lysates as cancer vaccines to inhibit the growth of or kill established cancers, such strategies have shown limited success and the instant application has presented no evidence that such "cancer vaccines" or "autologous tumor vaccine" would be effective in combination with a 2.13.2 antibody. For example, Oettgen et al (Biologic Therapy of Cancer, Chapter 6:87-119, 1991) teach that while "[t]he idea of a human cancer vaccine is as old as immunologic thought itself, and has a history that extends back more than two centuries", cancer vaccination trials in general "did not produce convincing evidence

of therapeutic efficacy when they were appropriately controlled" (see page 967, right column). Furthermore, Oettgen et al teach that autologous cancer vaccines only produce antibody responses "in exceptional patients" (see page 96, right column). Notably, in this case, the specification presents no "cancer vaccines" or "autologous tumor vaccine" which has been used to effectively inhibit the progress of any multiple myeloma cancer or any other cancer, and the art teaches that it is highly unpredictable whether any autologous tumor vaccine or cancer vaccine would be effective to inhibit the growth of or kill established cancers. Therefore, it is submitted that one of skill in the art could not immediately envision recognize or predict the "cancer vaccines" or "autologous tumor vaccine" which could be used in combination with a "2.13.2" in the claimed methods.

Finally, with respect to the anti-proliferative agent being a "PDGFR inhibitor", the genus of "PDGFR inhibitors" are not described as having any structural or functional similarity with other members of the genus of "PDGFR inhibitors" besides their implied ability to inhibit PDGFR. Furthermore, since these inhibitors include structurally and functionally diverse members that include compounds such as antibodies and small molecules, it is submitted that this genus does not have any particularly identifying (i.e., substantial) structural feature that correlates with their implied function of being a PDGFR inhibitor. Notably, the specification fails to adequately describe this genus as there is no disclosure of any particularly identifying (i.e., substantial) structural feature that is shared by the members of this genus, which correlates with any particularly identifying functional feature also shared by at least a substantial number of those members. As a consequence, the disclosure would not reasonably convey that Applicant had possession of the claimed invention at the time the application was filed because the disclosure would not permit the skilled artisan to immediately envision, recognize or distinguish members of the genus of "PDGFR inhibitor"," from any other.

Notably, while Martinelli et al (Haem., 86:908-917, 2001) describe species of PDGFR inhibitors, i.e., SU5416 and SU6668 as molecular therapies for multiple myeloma (see entire document, e.g., abstract and pages 914 and 915, because PDGFR inhibitors are structurally and functionally diverse compounds which are not

generally identified in the art as having any particularly identifying (i.e., substantial) structural feature that is shared by the members of this genus, it is submitted that one of skill in the art would not be able to immediately evasion, recognize or distinguish the "PDGFR inhibitors" to which the claims are directed and one of skill in the art would not conclude that Applicant was in possession of the claimed genus to administer to mammals.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to methods that administer a genus of structurally disparate "antibodies" "vaccines", and "PDGFR inhibitors" an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction

to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

In summary, given the lack of particularity with which the claimed methods which administer structurally and functionally diverse "2.13.2" antibodies "vaccines", and "PDGFR inhibitors", are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed "2.13.2" antibodies "vaccines", and "PDGFR inhibitors, to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

18. Claims 1 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method of inhibiting the progress of multiple myeloma in a patient with multiple myeloma expressing human IGF-IR antigen, said method comprising administering to the patient an amount of a 2.13.2 human anti-IGF-IR antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a light chain comprising the amino acid sequence of SEQ ID NO: 47 effective to inhibit the progress of said multiple myeloma in combination with an anti-emetic, an analgesic, an anti-vascular agent, and an anti-proliferative agent, whereby the progression of multiple myeloma in the patient is inhibited, **and while being enabling for using** any methods encompassed by the claims, which have been taught by the prior art, **does not reasonably provide enablement for making and using** the full scope of the claimed methods. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In the instant case, the claims are In the instant case, the claims are broadly drawn to a diverse genus of methods that administer a structurally and functionally diverse genus of antibodies designated “2.13.2” in an effective amount to a mammal in combination with an agent selected from the group consisting of a anti-emetic, cancer vaccine, analgesic, anti-vascular agent, and anti-proliferative agent with the stated

objective of “treating” multiple myeloma. As drawn to the elected species of " vaccine" claim 5, recites administering a structurally and functionally diverse genus of “autologous tumor vaccines”. As drawn to the elected species of "anti-proliferative agent" claim 8, recites administering a structurally and functionally diverse genus of “PDGFR inhibitors”.

Notably, the scope of the term “treating” is being broadly, but reasonably interpreted as including “preventing” a disorder because the mammal need not have any disorder and in light of the following disclosure at page 6 which sets forth that treating encompasses preventing:

> The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or **preventing** the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

As a first point, wherein the claims encompass the **prevention** of multiple myeloma**,** the specification does not enable the use of any of the recited methods for the prevention of multiple myeloma. In this case, the prevention of multiple myeloma, i.e., keeping individuals free of any multiple myeloma indefinitely, is an intractable proposition, if not now wholly impossible, given, for example, that multiple myeloma is a heterogeneous disease, having widely varying pathologies and etiologies, and that its causes are multifactorial and as yet only partially characterized and poorly understood. It is generally recognized that a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development by any cause. Notably, in this case, the specification presents merely prophetic examples that administering to a mammal the recited combinations would be effective to prevent multiple myeloma (see e.g., page 2). As such, the specification, which lacks any specific non-general guidance, direction, and exemplification that is reasonably commensurate in scope with the breadth of the claims, would not reasonably enable the artisan to use the claimed invention to prevent

multiple myeloma without undue and/or unreasonable experimentation, for example, by prophylactically administering to a mammal any of the recited combinations.

Here, there is no disclosure of testing using any model to determine if any of the recited combinations prevent multiple myeloma in any mammal; again, the assertion that the invention is useful is based solely upon merely prophetic examples that administering to a mammal such combinations would be effective to prevent multiple myeloma.

Secondly, with respect to the structurally and functionally diverse genus of "2.13.2" antibodies, which encompasses any antibody that could be derived from a hybridoma of the same name, including antibodies comprising only a fragment of another antibody, as set forth in the above rejection of the claims under, 35 USC 112, first paragraph, since the claims are not limited to antibodies or antigen-binding fragments which have been adequately described, the skilled artisan could also not envision, recognize or distinguish the claimed antibodies which would be effective in the claimed methods. Moreover, absent a sufficiently detailed description of antibodies, the skilled artisan could not make antibodies without undue and/or unreasonable experimentation; and if the antibodies cannot be made without undue and/or unreasonable experimentation, the specification would not reasonably enable the skilled artisan use these antibodies without undue and/or unreasonable experimentation in the claimed methods. For example, because the claims encompass administration to any mammal, including mammals that have multiple myeloma which do not express the human IGF-IR antigen, one of skill in the art would be subject to undue experimentation to use any "2.13.2" antibody in these mammals to achieve the recited objective, because the specification does not present any specific guidance as to how to make a "2.13.2" antibody target cells not expressing the human IGF-IR antigen.

Additionally, because one skilled in the art could not make the claimed antibodies without undue and/or unreasonable experimentation, the specification would not reasonably enable one to *use* the claimed antibodies, since only that which can be made can be used, and what cannot be made cannot be used.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable domains of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979-1983). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies that do not contain all of the 6 CDRs of the parent monoclonal antibody in their proper context of heavy and light chain variable domains, respectively, would retain the epitope-binding function of the parent antibody. For this reason, the specification would not reasonably enable the skilled artisan to use the full scope of the claimed invention at the time the application was filed without undue and/or unreasonable.

Then to address the enablement of “cancer vaccines” or “autologous tumor vaccine” set forth in the claimed methods which are to be used in combination with a “2.13.2” antibody, while the art is replete with attempts to use autologous cancer cell lysates as cancer vaccines to inhibit the growth of or kill established cancers, such strategies have shown limited success and the instant application has presented no evidence that such “cancer vaccines” or “autologous tumor vaccine” would be effective in combination with a 2.13.2 antibody. For example, Oettgen et al (Biologic Therapy of Cancer, Chapter 6:87-119, 1991) teach that while “[t]he idea of a human cancer vaccine

is as old as immunologic thought itself, and has a history that extends back more than two centuries", cancer vaccination trials in general "did not produce convincing evidence of therapeutic efficacy when they were appropriately controlled" (see page 967, right column). Furthermore, Oettgen et al teach that autologous cancer vaccines only produce antibody responses "in exceptional patients" (see page 96, right column). Notably, in this case, the specification presents no "cancer vaccines" or "autologous tumor vaccine" which has been used to effectively inhibit the progress of any multiple myeloma cancer or any other cancer, and the art teaches that it is highly unpredictable whether any autologous tumor vaccine or cancer vaccine would be effective to inhibit the growth of or kill established cancers. Therefore, it is submitted that one of skill in the art would be subject to undue experimentation to use "cancer vaccines" or "autologous tumor vaccines" in combination with a "2.13.2" antibody in the claimed methods to achieve the claimed objective.

Finally, with respect to the anti-proliferative agent being a "PDGFR inhibitor", while Martinelli et al (Haem., 86:908-917, 2001) describe species of PDGFR inhibitor, i.e., SU5416 and SU6668, as molecular therapies for multiple myeloma (see entire document, e.g., abstract and pages 914 and 915, because PDGFR inhibitors are structurally and functionally diverse compounds which are not generally identified in the art as being effective to inhibit the progression of multiple myeloma and because the specification presents no specific, non-general guidance as to how to make "PDGFR inhibitors" which could be effectively used in the claimed methods it is submitted that one of skill in the art would also be subject to undue experimentation to use the full scope of "PDGFR inhibitors" in the clamed methods.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be

provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful and full consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claims 1 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Cohen et al (WO 02/053596: published 07/11/2002, IDS filed 12/08/2004), as evidenced by Martinelli et al (Haem., 86:908-917, 2001) and Giles (Onc., 6(Sup5):32-39, 2001).

The clams are herein drawn to methods that administer a "2.13.2" antibody to a mammal in combination with an agent selected from the group consisting of an anti-vascular agent and an anti-proliferative agent. Claim 8 further recites that the "anti-proliferative agent" is "PDGFR inhibitors". Notably, as set forth in the above rejection of the claims under 35 USC 112, first paragraph, the claims do not require that the

antibody be administered to a mammal with multiple myeloma and therefore the intended use, i.e., "treatment of multiple myeloma" is not being given patentable weight. This position is further supported because the claims do not recite what the amount of the antibody must be effective to achieve as explained in the above rejection of the claims under 35 USC, 112, second paragraph. Accordingly, the claims are being broadly, but reasonably interpreted as encompassing any methods that administer a "2.13.2" antibody to a mammal in combination with an agent selected from the group consisting an anti-vascular agent and an anti-proliferative agent.

Cohen et al teach methods that administer a 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a mammal having a cancer in combination with anti-neoplastic agents such as a anti-vascular agent, or a anti-proliferative agent which is a PDGFR inhibitor such as SU5416 and SU6668 (see entire document, pages 7, 63 and 69-72). While Cohen et al do not characterize SU5416 and SU6668 as PDGFR inhibitors, as evidenced by Martinelli et al (Haem., 86:908-917, 2001) and Giles (Onc., 6(Sup5):32-39, 2001) these molecules are known in the art to be PDGFR inhibitors (see Martinelli entire document, e.g., abstract and pages 914 and 915) and Giles entire document, e.g., page 36).

In summary, the processes of Cohen et al are materially and manipulatively indistinguishable from the claimed process and therefore, absent a showing of any difference, the process disclosed by the prior art are deemed the same as the claimed process and Cohen et al anticipate the claimed process

21. Claims 1 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al (b) (US Patent 7,037,498, application filed 2/4/02), as evidenced by Martinelli et al (Haem., 86:908-917, 2001) and Giles (Onc., 6(Sup5):32-39, 2001).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The clams are herein drawn to methods that administer a "2.13.2" antibody to a mammal in combination with an agent selected from the group consisting of an anti-vascular agent and an anti-proliferative agent. Claim 8 further recites that the "anti-proliferative agent" is "PDGFR inhibitors". Notably, as set forth in the above rejection of the claims under 35 USC 112, first paragraph, the claims do not require that the antibody be administered to a mammal with multiple myeloma and therefore the intended use, i.e., "treatment of multiple myeloma" is not being given patentable weight. This position is further support because the claims do not recite what the amount of the antibody must be effective to achieve as explained in the above rejection of the claims under 35 USC, 112, second paragraph. Accordingly, the claims are being broadly, but reasonably interpreted as encompassing any methods that administer a "2.13.2" antibody to a mammal in combination with an agent selected from the group consisting an anti-vascular agent and an anti-proliferative agent.

Cohen et al (b) teach methods that administer a 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a mammal having a cancer in combination with anti-neoplastic agents such as a anti-vascular agent, or a anti-proliferative agent which is a PDGFR inhibitor such as SU5416 and SU6668 (see entire document, column 5, 44 and 46-50). Cohen et al (b) also exemplifies patients having multiple myeloma as patients to which such a 2.13.2 antibody can be administered (see column 24). While Cohen et al (b) do not characterize SU5416 and SU6668 as PDGFR inhibitors, as evidenced by Martinelli et al (Haem., 86:908-917, 2001) and Giles (Onc., 6(Sup5):32-39, 2001) these molecules are known in the art to be PDGFR inhibitors (see Martinelli entire document, e.g., abstract and pages 914 and 915) and Giles entire document, e.g., page 36).

In summary, the processes of Cohen et al (b) are materially and manipulatively indistinguishable from the claimed process and therefore, absent a showing of any

difference, the process disclosed by the prior art are deemed the same as the claimed process and Cohen et al anticipate the claimed process.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (WO 02/053596: published 07/11/2002, IDS filed 12/08/2004) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) as

evidenced by Martinelli et al (Haem., 86:908-917, 2001) and Giles (Onc., 6(Sup5):32-39, 2001).

For this rejection, the claims herein are drawn to methods that administer a "2.13.2" antibody to a mammal having multiple myeloma in combination with an agent selected from the group consisting of an anti-vascular agent and an anti-proliferative agent. Claim 8 further recites that the "anti-proliferative agent" is "PDGFR inhibitors".

Cohen et al teach what is set forth in the above rejection of the claims under 35 USC 102(b). Cohen et al do not expressly teach patients with multiple myeloma expressing human IGF-IR.

This deficiency is made up for in the teachings of Mitsaides et al. Mitsaides et al teach 10 out of 10 multiple myeloma patients strongly express human IGF-IR and that an inhibitory anti-IGR-IR antibody was effective in blocking survival pathways in these cells (see abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a patient with multiple myeloma in combination with anti-neoplastic agents such as a anti-vascular agent, or a anti-proliferative agent which is a PDGFR inhibitor such as SU5416 and SU6668.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because Cohen et al teach that said 2.13.2 antibody is effective at inhibiting the growth of cancers expressing human IGF-IR and because Mitsaides et al teaches patients with multiple myeloma that express human IGF-IR and whose cells are sensitive to an inhibitory anti-IGR-IR antibody. Furthermore, as evidenced by Martinelli et al and Giles the PDGFR inhibitors taught by Cohen et al also are molecular therapies which would be effective in a patient with multiple myeloma. Therefore, one of skill in the art would have reasonably expected such methods to be effective at inhibiting the growth of multiple myeloma in patients as the art teaches that such methods of administering an

inhibitory anti-IGR-IR antibody in combination with PDGFR inhibitors would predictably inhibit the growth of multiple myeloma. For these reasons, one of skill in the art would have not found it inventive to administer said 2.13.2 antibody in combination with the PDGFR inhibitors taught by Cohen et al to patients having multiple myeloma expressing IGF-IR.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

25. Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (WO 02/053596: published 07/11/2002, IDS filed 12/08/2004) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Giles (Onc., 6(Sup5):32-39, 2001).

For this rejection, the claims are herein drawn to methods that administer a "2.13.2" antibody to a mammal having multiple myeloma in combination with bevacizumab.

Cohen et al and Mitsaides et al teach what is set forth in the above rejection of the claims under 35 USC 103(a). While these references suggest administering the 2.13.2 antibody of Cohen et al in combination with other therapies which are effective to inhibit the growth of multiple myeloma in a patient, they do not expressly teach bevacizumab as such a therapy.

This deficiency is made up for in the teachings of Giles et al. Giles et al teach that angiogenesis is important in multiple myeloma and other hematologic malignancies and that anti-vascular factors such as bevacizumab which inhibits angiogenesis have shown potent anti-tumor activities (see entire document, e.g., abstract, pages 32, and 36-38).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a

heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a patient with multiple myeloma in combination with bevacizumab.

In this case, because the art recognizes that inhibiting human IGF-IR with said 2.13.2 antibody would predictably inhibit the growth of multiple myeloma expressing human IGF-IR and that angiogenesis was important in multiple myeloma and could be inhibited with bevacizumab, one of skill in the art would have reasonable expected that such combinations would inhibit the growth of multiple myeloma and would have been motivated to administer both agents in combination to achieve the most effective results in patients with multiple myeloma.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

26. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (WO 02/053596: published 07/11/2002, IDS filed 12/08/2004) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Manfredi et al (Can., 89(4):920-924, 2000).

For this rejection, the claims are herein drawn to methods that administer a "2.13.2" antibody to a mammal having multiple myeloma in combination with an anti emetic or analgesic such as ibuprofen, naproxen, choline magnesium trisalicylate or oxycodone.

Cohen et al and Mitsaides et al teach what is set forth in the above rejection of the claims under 35 USC 103(a). While these references suggest administering the 2.13.2 antibody of Cohen et al in combination with other therapies, they do not expressly teach managing nausea or pain in multiple myeloma patients.

This deficiency is made up for in the teachings of Manfredi et al. Manfredi et al teach that it is common for cancer patients to suffer from nausea which can be managed as needed by antiemetics and that it is common for cancer patients to suffer from pain which can be managed as needed by analgesics such as ibuprofen, naproxen, choline magnesium trisalicylate or oxycodone (see entire document, e.g., abstract and page 921). Furthermore, Manfredi et al teach that multiple myeloma

patients would be included in the genus of cancer patients which would need such treatments (see Table 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a patient with multiple myeloma in combination with an anti emetic or analgesic such as ibuprofen, naproxen, choline magnesium trisalicylate or oxycodone.

In this case, because the art recognizes that cancer patients suffer from nausea and pain one of skill in the art would have been motivated to also administer such agents in combination the antibody of Cohen et al to relieve nausea and pain. Furthermore, since these agents are widely used for such purposes in cancer patients one of skill in the art would have reasonably expected such agents to work in patients that had been administered the 2.13.2 antibody of Cohen.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

27. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (WO 02/053596: published 07/11/2002, IDS filed 12/08/2004) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Manfredi et al (Can., 89(4):920-924, 2000) as applied to claim 1 above, and further in view Groziak (US Patent 6,083,936, 2000),

Claim 4 is further drawn to the anti-emetic being ondansetron, granisetron, tropisetron or metoclopramide.

Groziak teaches that ondansetron, granisetron, tropisetron or metoclopramide are anti-emetics that can be used for nausea in cancer patients.

It would have been *prima facie* to administer the 2.13.2 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:45 and a heavy chain comprising the amino acid sequence of SEQ ID NO:47 to a patient with multiple

myeloma in combination with an anti-emetic such as ondansetron, granisetron, tropisetron or metoclopramide.

In this case, because the art recognizes that cancer patients suffer from nausea and that anti-emetics such as ondansetron, granisetron, tropisetron or metoclopramide can alleviate nausea in cancer patients one of skill in the art would have been motivated to also administer such agents in combination the antibody of Cohen et al to relieve nausea. Furthermore, since these agents are widely used for such purposes in cancer patients one of skill in the art would have reasonably expected such agents to work in patients that had been administered the 2.13.2 antibody of Cohen.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

28. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

29. Claims 1 and 8 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 85 and 87 of US Patent No. 7,037,498 (Cohen et al, 2006). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are described supra.

Claims 85 and 87 of US Patent 7,037,498 are drawn to methods of treating a patient with cancer that expresses IGF-IR with an 2.13.2 antibody in combination with anti-angiogenic agent, and anti-neoplastic agent an anti-tumor agent or a chemotherapeutic agent.

While the claims do not further define the agents, it is noted that the specification of '498 discloses that SU5416 and SU6668 are such agents, which are known in the art to be PDGFR inhibitors (see entire document column 44).

Notably, MPEP § 804.II.B.1 states that when considering obviousness-type double patenting issues, the disclosure of the patent [or copending application] cannot be used as prior art, but "[t]his does not mean one is precluded from all use of the patent disclosure". MPEP § 804.II.B.1 continues, "[t]he specification can always be used as a dictionary to learn the meaning of a term in the patent [or application] claim". Citing *In re Vogel and Vogel*, 164 USPQ 619 (CCPA 1970), MPEP § 804.II.B.1 states, "one must first 'determine how much of the patent [or application] disclosure pertains to the invention claimed in the patent [or application]' because only '[t]his portion of the specification supports the patent claims and may be considered' " and " 'this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, **since only the disclosure of the invention claimed in the patent may be examined**" [emphasis added]. Consistently, in this instance, the examiner used only that portion of the copending application disclosure that pertains to the claimed invention.

Further addressing *In re Vogel and Vogel*, the Court decided the correctness of the conclusion that a patent claim drawn to a process for packaging "pork" would be obvious over a pending claim drawn to a process for packaging "meat", since although "pork does not read on "meat", "meat" reads literally on "pork". However, the Court

further noted "viewing the inventions in reverse order, i.e., as though the broader claims issued first, does not reveal that the narrower (pork) process is in any way unobvious over the broader (meat) invention disclosed and claimed in the instant application" *Id.* at 623. The examiner believes this is because, were the patent claim to broadly recite "meat", although "pork" does not read on "meat" (i.e., a species encompassed by the genus generally does not suffice to describe the genus), the specification states how the claimed process is to be carried out with "pork". The Court indicated that this portion of the specification, stating how the claimed process is to be carried out using pork, supports the patent claims *and may be considered*. *Id.* at 622.

In certain situations, the supporting disclosure may be used to define terms in a claim and to determine whether the invention claimed has been modified in an obvious or unobvious manner. See *Carman Industries, Inc. v. Wahl et al.*, 220 USPQ 481 (CA FC 1983). If modified in an unobvious manner, there is no double patenting issue. In this instance, there can be no mistake that the invention claimed in the instant application is an obvious "variant" of the invention claimed in the patent, because the supporting disclosure of the latter teaches that SU5416 and SU6668 are agents that would be encompassed by the terms anti-angiogenic agent, anti-neoplastic agent, an anti-tumor agent or a chemotherapeutic agent set forth in claim 87

If the instant claims were drawn instead to an unobvious "variant", or to an invention that might only be gleaned from consideration of portions of the disclosure that do not support the copending claims, such that the consideration would be improper, then there would be no double patenting issue. Because only those portions of the disclosure that support the copending claims has been considered, and those portions include a description of the "variant" claimed in the instant application, then, double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent.

30. Claims 1 and 7 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 85 and 87 of US Patent No. 7,037,498 (Cohen et al, 2006) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Giles (Onc., 6(Sup5):32-39, 2001).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are described *supra*.

Claims 85 and 87 of US Patent No. 7,037,498 are described supra.

In this case, while claims 85 and 87 of Us Patent 7,037,498 do not expressly teach administering a 2.13.2 antibody to a multiple myeloma patient along with bevacizumab, as detailed in the above rejection of the claims under 35 U.S.C. 103(a), based on the teachings of Mitsaides et al and Giles et al, administering a 2.13.2 antibody to a multiple myeloma patient along with bevacizumab would be considered an obvious variation of the method disclosed in Claims 85 and 87 of US Patent No. 7,037,498. If the instant claims were drawn instead to an unobvious "variant", then there would be no double patenting issue. However, since such methods would be considered an obvious variation of the methods of claims 85 and 87 of US Patent No. 7,037,498, then, this double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in US Patent 7,037,498.

31. Claims 1 and 6 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 85 and 87 of US Patent No. 7,037,498 (Cohen et al, 2006) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Manfredi et al (Can., 89(4):920-924, 2000).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are described *supra*.

Claims 85 and 87 of US Patent No. 7,037,498 are described supra.

In this case, while claims 85 and 87 of US Patent 7,037,498 do not expressly teach administering a 2.13.2 antibody to a multiple myeloma patient along with an anti emetic or analgesic such as ibuprofen, naproxen, choline magnesium trisalicylate or oxycodone, as detailed in the above rejection of the claims under 35 U.S.C. 103(a), based on the teachings of Mitsaides et al and Manfredi et al, administering a 2.13.2 antibody to a multiple myeloma patient along with an anti emetic or analgesic such as ibuprofen, naproxen, choline magnesium trisalicylate or oxycodone would be considered an obvious variation of the method disclosed in Claims 85 and 87 of US Patent No. 7,037,498. If the instant claims were drawn instead to an unobvious "variant", then there would be no double patenting issue. However, since such methods would be considered an obvious variation of the methods of claims 85 and 87 of US Patent No. 7,037,498, then, this double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in US Patent 7,037,498.

32. Claim 4 is rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 85 and 87 of US Patent No. 7,037,498 (Cohen et al, 2006) in view of Mitsaides et al (Blood, 100(11):170A, published 2002, IDS filed 12/08/2004) and Manfredi et al (Can., 89(4):920-924, 2000) as applied to claim 1 above, and further in view of Groziak (US Patent 6,083,936, 2000).

The instant claim is described *supra*.

Claims 85 and 87 of US Patent No. 7,037,498 are described supra.

In this case, while claims 85 and 87 of US Patent 7,037,498 do not expressly teach administering a 2.13.2 antibody to a multiple myeloma patient along with an anti emetic such as ondansetron, granisetron, tropisetron or metoclopramide, as detailed in the above rejection of the claims under 35 U.S.C. 103(a), based on the teachings of

Mitsaides et al, Manfredi et al and Groziak administering a 2.13.2 antibody to a multiple myeloma patient along with an anti emetic such as ondansetron, granisetron, tropisetron or metoclopramide, would be considered an obvious variation of the method disclosed in Claims 85 and 87 of US Patent No. 7,037,498. If the instant claims were drawn instead to an unobvious "variant", then there would be no double patenting issue. However, since such methods would be considered an obvious variation of the methods of claims 85 and 87 of US Patent No. 7,037,498, then, this double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in US Patent 7,037,498.

Conclusion

33. No claims are allowed.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
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